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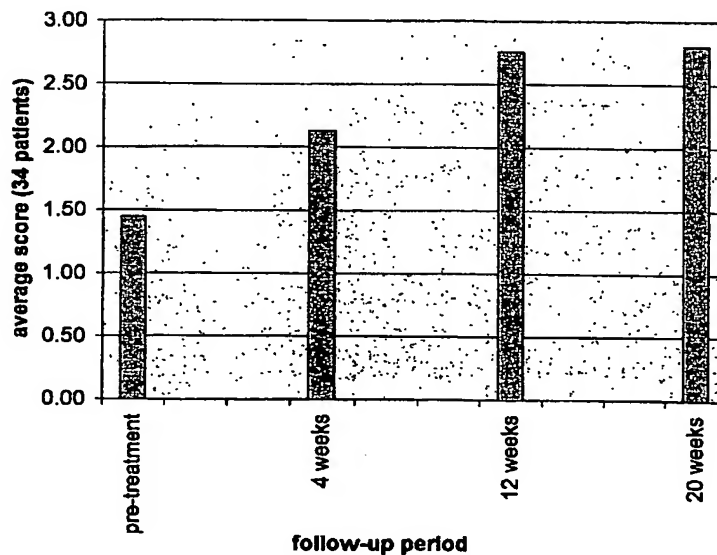
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(54) Title: OSTEOINDUCTIVE BIOMATERIALS

X-RAY EVALUATION SCORES



(57) Abstract: In a method of isolating osteogenic protein from bone, in which an osteogenic protein containing fraction is extracted from bone and enriched by a sequence of enrichment steps selected from ultrafiltration and chromatography, the invention provides the improvement of removing higher molecular weight components from the osteogenic protein containing fraction prior to the enrichment steps. The higher molecular weight components have a molecular weight of about 100 - 300 kDa and are selected from collagen, collagen fragments, collagen aggregates and mixtures thereof.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 03/02354-0

CLASSIFICATION OF SUBJECT MATTER

IPC⁷: C07K 14/47, 1/36, A61K 35/32 // (C07K 1/36, C07K 1:34, C07K 1:16)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC⁷: C07K, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, EPO, PAJ, REGISTRY, CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	M. R. URIST et al., "Purification of bovine bone morphogenetic protein by hydroxyapatite chromatography", Proc. Natl. Acad. Sci., 81, 1984, pages 371-375 <i>the whole document.</i>	1-3
X	C. KELLY SCOTT et al., "Intramembranous Bone Matrix Is Osteoinductive", The Anatomical Record, 238, 1994, pages 23-30 <i>the whole document, esp. pages 23, 24 (left column), 27-29.</i>	1-6
X	Y. YOSHIMURA et al., "Purification of Water-Soluble Bone-Inductive Protein from Bovine Demineralized Bone Matrix", Biol. Pharm. Bull., 16 (5), 1993, pages 444-447 <i>the whole document.</i>	1-6
A	EP 0474174 A2 (TAKEDA CHEMICAL INDUSTRIES LTD.) 11 March 1992 (11.03.1992) <i>the whole document, esp. claims, examples.</i>	1-6,8- 10,12,14-16

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

„A“ document defining the general state of the art which is not considered to be of particular relevance

„E“ earlier application or patent but published on or after the international filing date

„L“ document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

„O“ document referring to an oral disclosure, use, exhibition or other means

„P“ document published prior to the international filing date but later than the priority date claimed

„T“ later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

„X“ document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

„Y“ document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

„&“ document member of the same patent family

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 1999/038543 A2 (REGENERATION TECHNOLOGIES, INC. et al.) 5 August 1999 (05.08.1999) ; <i>the whole document.</i>	7-12
X	WO 1998/040113 A1 (UNIVERSITY OF FLORIDA TISSUE BANK, INC. et al.), 17 September 1998 (17.09.1998) <i>the whole document.</i>	7-12
X	WO 1996/039203 A1 (BIOCOLL LABORATORIES, INC.) 12 December 1996 (12.12.1996) <i>the whole document, esp. claims.</i>	7-12
X	US 6030635 A (A. A. GERTZMAN et al.) 29 February 2000 (29.02.2000) <i>the whole document.</i>	7-12

INTERNATIONAL SEARCH REPORT

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 13-16
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The "device" to which claims 13-16 are directed is not characterized clearly and concisely, esp. due to the use of undefined terms like "delivery mechanism for delivery of..", "treatment site", "device for.. including a bone growth inducing composition which comprises..". Therefore, these claims merely describe the problem to be solved and not a technical "device" suitable to solving it.
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Group I, claims 1-6, 8-10 (partly), 12 (partly), 14-16 (partly), directed to a particular method of isolating osteogenic protein from bone, a bone growth inducing composition comprising the osteogenic protein isolated by the method of claim 1-6 and a device for inducing bone growth in a mammal comprising said bone growth inducing composition.

Group II, claims 7, 11 and 13, as well as claims 8-10 (partly), 12 (partly) and 14-16 (partly), directed to a bone growth inducing composition which includes osteogenic protein, insoluble bone matrix and gelatin, a method for preparing such a composition and a device for inducing bone growth comprising such a composition.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Remarks:

- 1) The word "including" in the present claims 7, 8, 11 and 13 is not used formally correct, since it is - due to its broad character - not suited to characterize a chemical composition or a chemical process clearly and concisely.
- 2) In claim 11 reaction or process "steps" are mentioned, but there can only be identified one single step of mixing three components. This discrepancy should be avoided.
- 3) The terms "delivery mechanism" and "treatment site" are too broad to describe the subject matter of claim 13 clearly and concisely and should thus be clarified.
- 4) Claim 1 is not formulated correctly, since the characteristic part of this claim may not be written in the form "the improvement of removing..".
- 5) It should be clarified in the claims, esp. in claim 1, that ultrafiltration is used to remove the high molecular weight components before the enrichment steps and that ultrafiltration is one possible method used as enrichment method, as well. Further, these two "kinds" of ultrafiltration should be distinguished clearly in the claims.
- 6) The relative and thus broad term "higher molecular weight components" in claim 1 should be formulated more precisely.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/IB 03/02354-0

Patent document cited in search report			Publication date		Patent family member(s)	Publication date
A					none	
EP	A	474174			US A 5244577	1993-09-14
					US A 5183570	1993-02-02
					EP A 0474174	1992-03-11
					CA A 2050744	1992-03-07
					AU A 8361991	1992-03-12
					JP A 5085939	1993-04-06
US	A	6030635			US E RE385228	2004-05-25
					US A 2003206937	2003-11-06
					CA A 2294686	2001-07-06
					US A 2002197242	2002-12-26
					US A 2002192263	2002-12-19
					US B 6458375	2002-10-01
WO	A	19960392			none	
		03				
WO	A	19980401			none	
		13				